

Application No. 10/735,607
 Amendment dated November 7, 2006
 Reply to Office Action dated August 9, 2006

Docket No.: 60427 (72021)

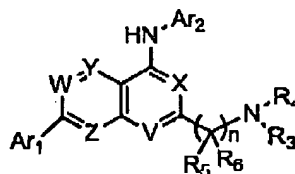
AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

1-40. (Cancelled)

41. (Currently amended) A compound of the formula:



or a pharmaceutically acceptable formsalt or hydrate thereof, wherein:

V, X and Z are N;

W and Y are CR₁;

R₁ is independently selected at each occurrence from hydrogen, halogen, hydroxy, cyano, amino, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₁-C₄alkoxycarbonyl and mono- and di-(C₁-C₆alkyl)amino;

R₃ and R₄ are:

(i) each independently selected from:

(a) hydrogen;

(b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₃-C₈alkanone, C₂-C₈alkanoyl, C₂-C₈alkyl ether, (C₆-C₁₀aryl)C₀-C₈alkyl, (5- to 10-membered heterocycle)C₀-C₈alkyl and -(SO₂)C₁-C₈alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from R_b; and

(c) groups that are taken together with an R₅ or R₆ to form a 4- to 10-membered heterocycle that is substituted with from 0 to 4 substituents independently chosen from R_b; or

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(ii) taken together to form a 4- to 10-membered heterocycle that is substituted with from 0 to 4 substituents independently chosen from R_b ;

R_5 and R_6 are, independently at each occurrence:

- (i) each independently hydrogen, C_1 - C_8 alkyl substituted with from 0 to 2 substituents independently chosen from R_b , or taken together with R_3 or R_4 to form a 4- to 10-membered heterocyclic group that is substituted with from 0 to 4 substituents independently chosen from R_b ;
- (ii) taken together to form a keto group; or
- (iii) taken together to form a 3- to 7-membered carbocyclic or heterocyclic ring that is substituted with from 0 to 4 substituents independently chosen from R_b ;

n is 1, 2 or 3;

Ar_1 and Ar_2 are independently selected from ~~6- to 10-membered aryl groups and 5- to 10-membered heterocycles~~ phenyl or pyridyl, each of which is substituted with from 0 to 3 substituents independently selected from groups of the formula LR_a ;

L is independently selected at each occurrence from a bond, O, $S(O)_m$, $C(=O)$, $OC(=O)$, $C(=O)O$, $O-C(=O)O$, $N(R_x)$, $C(=O)N(R_x)$, $N(R_x)C(=O)$, $N(R_x)S(O)_m$, $S(O)_mN(R_x)$ and $N[S(O)_mR_x]S(O)_m$; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C_1 - C_8 alkyl;

R_a is independently selected at each occurrence from: (i) hydrogen, halogen, cyano and nitro; and (ii) C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, C_2 - C_8 alkyl ether, (4- to 10-membered heterocycle) C_0 - C_8 alkyl and mono- and di- $(C_1$ - C_8 alkyl)amino, each of which is substituted with from 0 to 4 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, oxo, $-COOH$, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, halo C_1 - C_4 alkyl, halo C_1 - C_4 alkoxy, hydroxy C_1 - C_4 alkyl, and mono- and di- $(C_1$ - C_8 alkyl)amino; and

R_b is independently chosen at each occurrence from:

- (i) hydroxy, halogen, amino, aminocarbonyl, cyano, nitro, oxo and $-COOH$; and
- (ii) C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, C_1 - C_8 alkoxy, C_1 - C_8 haloalkoxy, C_1 - C_8 alkanoyl, C_2 - C_8 alkoxycarbonyl, C_2 - C_8 alkanoyloxy, C_1 - C_8 alkylthio, C_2 - C_8 alkyl ether, phenyl C_0 - C_8 alkyl, phenyl C_0 - C_8 alkoxy, mono- and di- $(C_1$ - C_8 alkyl)amino C_0 - C_8 alkyl, -

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(SO₂)C₁-C₆alkyl and (4- to 7-membered heterocycle)(C₀-C₆alkyl); each of which is substituted with from 0 to 3 substituents independently chosen from hydroxy, halogen, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy, hydroxyC₁-C₄alkyl, haloC₁-C₄alkyl, and mono- and di-(C₁-C₄alkyl)amino.

42-45. (Cancelled)

46. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 41, wherein Z is N and W and Y are each CH.

47. (Cancelled)

48. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 41, wherein Ar₁ and Ar₂ are independently selected from phenyl and ~~6-membered aromatic heterocycles~~ pyridyl, each of which is substituted with 0, 1 or 2 substituents.

49. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 48, wherein:

Ar₁ is phenyl or pyridyl, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy, cyano, amino, nitro, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy and haloC₁-C₆alkoxy; and

Ar₂ is phenyl or pyridyl, each of which is substituted with from 0 to 2 substituents independently selected from halogen, hydroxy, cyano, amino, nitro, mono- and di-(C₁-C₆alkyl)amino, C₁-C₆alkyl, haloC₁-C₆alkyl, cyanoC₁-C₆alkyl, C₁-C₆alkoxy, haloC₁-C₆alkoxy, C₂-C₆alkyl ether, C₁-C₆alkanoyl, -(SO₂)R_d, -N(R_x)S(O)_mR_d, and -N[S(O)_mR_x]S(O)_mR_d; wherein m is 1 or 2, R_x is hydrogen or C₁-C₆alkyl, and R_d is C₁-C₆alkyl, haloC₁-C₆alkyl, amino, mono- or di-(C₁-C₆alkyl)amino or a 5- to 10-membered, N-linked heterocyclic group, each of which R_d is substituted with from 0

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to 2 substituents independently chosen from halogen, hydroxy, cyano, amino, nitro, mono- and di-(C₁-C₆alkyl)amino, C₁-C₄alkyl, haloC₁-C₄alkyl, C₁-C₄alkoxy and haloC₁-C₄alkoxy.

50. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 49, wherein:

Ar₁ is pyridyl, unsubstituted or substituted with halogen, cyano, C₁-C₄alkyl or haloC₁-C₄alkyl; and

Ar₂ is phenyl or pyridyl, substituted with from 0 to 2 substituents independently chosen from halogen, C₁-C₄alkyl, cyanoC₁-C₄alkyl, haloC₁-C₄alkyl, C₂-C₆alkyl ether and groups of the formula -(SO₂)R_d, wherein R_d is C₁-C₄alkyl or haloC₁-C₄alkyl.

51. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 49, wherein:

Ar₁ is phenyl, unsubstituted or substituted with halogen, cyano, C₁-C₄alkyl or haloC₁-C₄alkyl; and

Ar₂ is phenyl or pyridyl, substituted with from 0 to 2 substituents independently chosen from halogen, C₁-C₄alkyl, cyanoC₁-C₄alkyl, haloC₁-C₄alkyl, C₂-C₆alkyl ether and groups of the formula -(SO₂)R_d, wherein R_d is C₁-C₄alkyl or haloC₁-C₄alkyl.

52. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 49, wherein:

Ar₁ is pyridin-2-yl, 3-methyl-pyridin-2-yl, 3-trifluoromethyl-pyridin-2-yl or 3-halo-pyridin-2-yl; and

Ar₂ is phenyl, pyridin-2-yl or pyridin-3-yl, each of which is substituted at the *para*-position with halogen, cyano, methyl, ethyl, propyl, isopropyl, *t*-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trifluoro-1-methyl-ethyl, methanesulfonyl, ethanesulfonyl, propanesulfonyl, propane-2-sulfonyl, trifluoromethanesulfonyl or 2,2,2-trifluoroethanesulfonyl.

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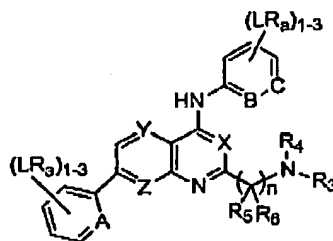
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53. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 49, wherein:

Ar₁ is phenyl, 2-methyl-phenyl, 2-trifluoromethyl-phenyl or 2-halo-phenyl; and

Ar₂ is phenyl, pyridin-2-yl or pyridin-3-yl, each of which is substituted at the *para*-position with halogen, cyano, methyl, ethyl, propyl, isopropyl, *t*-butyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trifluoro-1-methyl-ethyl, methanesulfonyl, ethanesulfonyl, propanesulfonyl, propane-2-sulfonyl, trifluoromethanesulfonyl or 2,2,2-trifluoroethanesulfonyl.

54. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 41, having the formula:



wherein A, B, and C are each independently CH or N, provided that B and C are not both N; Y is CH; Z is N, and wherein each "(LR_a)₁₋₃" represents from 1 to 3 substituents independently chosen from groups of the formula LR_a.

55. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 41, wherein R₃ and R₄ are independently selected from (i) hydrogen and (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₃-C₈alkanone, C₁-C₈alkanoyl, C₂-C₈alkyl ether, (C₆-C₁₀aryl)C₀-C₈alkyl, (5- to 10-membered heterocycle)C₀-C₈alkyl and -(SO₂)C₁-C₈alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from R₆.

56. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 55, wherein R₃ and R₄ are independently selected from (i) hydrogen and (ii) C₁-C₈alkyl, C₂-C₈alkenyl, phenylC₀-C₄alkyl,

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indanyl(C₀-C₄alkyl, (5- to 6-membered heteroaryl)C₀-C₄alkyl and (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 4 substituents independently selected from hydroxy, halogen, amino, C₁-C₆alkyl, haloC₁-C₆alkyl, C₁-C₆alkoxy and haloC₁-C₆alkoxy.

57. (Currently amended) A compound or pharmaceutically acceptable ~~formsalt or hydrate~~ thereof according to claim 56, wherein R₃ and R₄ are independently selected from hydrogen, C₁-C₆alkyl, C₂-C₆alkenyl, (5- to 7-membered heterocycle)C₀-C₄alkyl, C₂-C₆alkyl ether, indanyl, benzyl, 1-phenyl-ethyl, 1-phenyl-propyl and 2-phenyl-ethyl, each of which is substituted with from 0 to 3 substituents independently selected from hydroxy, halogen and C₁-C₄alkyl, with the proviso that at least one of R₃ and R₄ is not hydrogen.

58. (Currently amended) A compound or pharmaceutically acceptable ~~formsalt or hydrate~~ thereof according to claim 41, wherein one of R₃ or R₄ is taken together with an R₅ or R₆ to form a 4- to 10-membered heterocyclic group that is substituted with from 0 to 4 substituents independently selected from hydroxy, halogen, C₁-C₄alkyl, haloC₁-C₄alkyl, C₁-C₄alkoxy, haloC₁-C₄alkoxy, C₁-C₄alkanoyl, C₁-C₄alkoxycarbonyl, aminocarbonyl and (4- to 10-membered heterocycle)C₀-C₈alkyl.

59. (Currently amended) A compound or pharmaceutically acceptable ~~formsalt or hydrate~~ thereof according to claim 41, wherein R₃ and R₄ are taken together to form a 4- to 10-membered heterocycle that is substituted with from 0 to 4 substituents independently selected from hydroxy, halogen, aminocarbonyl, C₁-C₄alkyl, hydroxyC₁-C₄alkyl, haloC₁-C₄alkyl, C₁-C₄alkoxy, haloC₁-C₄alkoxy, C₁-C₄alkanoyl, C₂-C₄alkoxycarbonyl, aminocarbonyl and (4- to 7-membered heterocycle)C₀-C₈alkyl.

60. (Currently amended) A compound or pharmaceutically acceptable ~~formsalt or hydrate~~ thereof according to claim 59, wherein the 4- to 10-membered heterocycle is morpholinyl, piperidinyl, piperazinyl, pyrrolidinyl or thiomorpholinyl.

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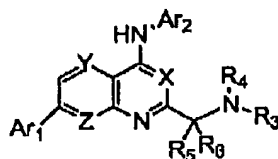
61. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 41, wherein each R_5 and R_6 is independently selected from hydrogen and C_1 - C_4 alkyl.

62. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 61, wherein each R_5 and R_6 is hydrogen.

63. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 41, wherein one R_5 and one R_6 attached to the same carbon atom are taken together to form a keto group.

64. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 41, wherein n is 1.

65. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 41, having the formula:



wherein:

Ar_1 is phenyl or pyridyl, unsubstituted or substituted with halogen, cyano, C_1 - C_4 alkyl or halo C_1 - C_4 alkyl;

Ar_2 is phenyl or pyridyl, unsubstituted or substituted with C_1 - C_4 alkyl, cyano C_1 - C_4 alkyl, halo C_1 - C_4 alkyl, C_2 - C_6 alkyl ether or a group of the formula $-(SO_2)R_d$, wherein R_d is C_1 - C_4 alkyl or halo C_1 - C_4 alkyl;

R_3 and R_4 are:

(a) independently selected from:

(i) hydrogen; and

(ii) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, (5- to 7-membered heterocycle) C_0 - C_4 alkyl, C_2 - C_6 alkyl ether, indanyl, benzyl, 1-phenyl-ethyl, 1-phenyl-propyl and 2-

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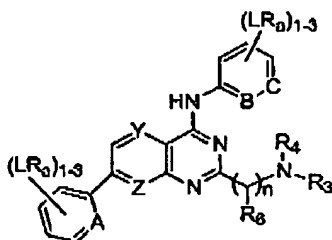
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phenyl-ethyl, each of which is substituted with from 0 to 3 substituents independently selected from hydroxy, cyano, halogen, C₁-C₄alkyl and haloC₁-C₄alkyl; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl that is substituted with from 0 to 3 substituents independently selected from hydroxy, cyano, halogen, C₁-C₄alkyl and haloC₁-C₄alkyl; and

R₅ and R₆ are independently selected from hydrogen and C₁-C₄alkyl.

66. (Currently amended) A compound or pharmaceutically acceptable formsalt or hydrate thereof according to claim 65, having the formula:



wherein:

A, B, and C are each independently CH or N, provided that B and C are not both N;

Y is CH;

Z is N;

R₃ and R₄ are:

(a) independently selected from:

(i) hydrogen; and

(ii) C₁-C₆alkyl, C₂-C₆alkenyl, (5- to 7-membered heterocycle)C₀-C₄alkyl, C₂-C₆alkyl ether, indanyl, benzyl, 1-phenyl-ethyl, 1-phenyl-propyl and 2-phenyl-ethyl, each of which is substituted with from 0 to 3 substituents independently selected from hydroxy, cyano, halogen, C₁-C₄alkyl and haloC₁-C₄alkyl; or

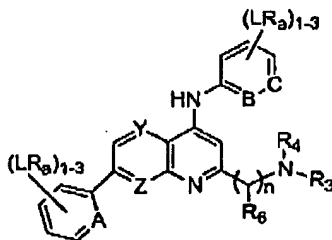
(b) taken together to form a 5- to 7-membered heterocycloalkyl that is substituted with from 0 to 3 substituents independently selected from hydroxy, cyano, halogen, C₁-C₄alkyl and haloC₁-C₄alkyl; and

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each R_6 is independently hydrogen or methyl.

67. (Currently amended) A compound or pharmaceutically acceptable form salt or hydrate thereof according to claim 65, having the formula:



wherein:

A, B, and C are each independently CH or N, provided that B and C are not both N;

Y is CH;

Z is N;

R_3 and R_4 are:

(a) independently selected from:

(i) hydrogen; and

(ii) C_1 - C_6 alkyl, C_2 - C_6 alkenyl, (5- to 7-membered heterocycle) C_0 - C_4 alkyl, C_2 - C_6 alkyl ether, indanyl, benzyl, 1-phenyl-ethyl, 1-phenyl-propyl and 2-phenyl-ethyl, each of which is substituted with from 0 to 3 substituents independently selected from hydroxy, cyano, halogen, C_1 - C_4 alkyl and halo C_1 - C_4 alkyl; or

(b) taken together to form a 5- to 7-membered heterocycloalkyl that is substituted with from 0 to 3 substituents independently selected from hydroxy, cyano, halogen, C_1 - C_4 alkyl and halo C_1 - C_4 alkyl; and

each R_6 is independently hydrogen or methyl.

68. (Cancelled)

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69. (Currently amended) A compound or pharmaceutically acceptable ~~form~~salt or hydrate thereof according to claim 41, wherein the compound has an IC₅₀ value of 100 nanomolar or less in a capsaicin receptor calcium mobilization assay.

70. (Currently amended) A compound or pharmaceutically acceptable ~~form~~salt or hydrate thereof according to claim 41, wherein the compound has an IC₅₀ value of 10 nanomolar or less in a capsaicin receptor calcium mobilization assay.

71. (Currently amended) A pharmaceutical composition, comprising at least one compound or pharmaceutically acceptable ~~form~~salt or hydrate thereof according to claim 41, in combination with a physiologically acceptable carrier or excipient.

72. (Original): A pharmaceutical composition according to claim 71 wherein the composition is formulated as an injectible fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup or a transdermal patch.

73-87. (Cancelled)

88. (Withdrawn) A method for treating pain in a patient, comprising administering to a patient suffering from pain a capsaicin receptor modulatory amount of at least one compound or pharmaceutically acceptable form thereof according to claim 41, and thereby alleviating pain in the patient.

89. (Withdrawn) A method according to claim 88, wherein the compound or pharmaceutically acceptable form thereof is present in the blood of the patient at a concentration of 1 micromolar or less.

90. (Withdrawn) A method according to claim 89, wherein the compound or pharmaceutically acceptable form thereof is present in the blood of the patient at a concentration of 500 nanomolar or less.

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91. (Withdrawn) A method according to claim 89, wherein the compound or pharmaceutically acceptable form thereof is present in the blood of the patient at a concentration of 100 nanomolar or less.

92. (Withdrawn) A method according to claim 88, wherein the patient is suffering from neuropathic pain.

93. (Withdrawn) A method according to claim 88, wherein the pain is associated with a condition selected from: postmastectomy pain syndrome, stump pain, phantom limb pain, oral neuropathic pain, toothache, postherpetic neuralgia, diabetic neuropathy, reflex sympathetic dystrophy, trigeminal neuralgia, osteoarthritis, rheumatoid arthritis, fibromyalgia, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome, bilateral peripheral neuropathy, causalgia, neuritis, neuronitis, neuralgia, AIDS-related neuropathy, MS-related neuropathy, spinal cord injury-related pain, surgery-related pain, musculoskeletal pain, back pain, headache, migraine, angina, labor, hemorrhoids, dyspepsia, Charcot's pains, intestinal gas, menstruation, cancer, venom exposure, irritable bowel syndrome, inflammatory bowel disease and trauma.

94. (Withdrawn) A method according to claim 88, wherein the patient is a human.

95-105. (Cancelled)